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An Open-Label Trial of the PPARγ Ligand Rosiglitazone for Active Ulcerative Colitis

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OBJECTIVES: Previous research has demonstrated that ligands for the γ subtype of peroxisome proliferator–activated receptors (PPARs) reduce inflammation in two different murine models of colitis. This study was designed to examine the potential efficacy of rosiglitazone, a ligand for the γ subtype of PPARs, as a therapy for active ulcerative colitis.

METHODS: Fifteen patients with mild to moderately active ulcerative colitis despite therapy with 5-aminosalicylic acid compounds were enrolled in an open-label study of rosiglitazone (4 mg *b.i.d. p.o.*) for 12 wk. Thirteen of 15 patients were receiving concomitant therapy with corticosteroids and/or immunomodulator medications. Disease activity was measured with the Disease Activity Index.

RESULTS: After 12 wk of therapy, four patients (27%) had achieved clinical remission, of whom three (20%) also had an endoscopic remission. Four additional patients (27%) had a clinical response without achieving remission. Two patients were hospitalized with worsened disease activity, and one patient was withdrawn for nephrotic syndrome.

CONCLUSIONS: These data suggest that ligands for the γ subtype of PPARs may represent a novel therapy for ulcerative colitis. A double blind, placebo-controlled, randomized trial is warranted. (Am J Gastroenterol 2001;96: 3323–3328. © 2001 by Am. Coll. of Gastroenterology)

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease involving all or a portion of the colon. There are few effective medical therapies for UC. Those currently available include oral or topically administered 5-aminosalicylic acid (5-ASA) agents and corticosteroids for mild to moderate disease and *i.v.* corticosteroids, immunomodulators such as azathioprine, 6-mercaptopurine, and cyclosporine, for more severe disease (1). Although 5-ASA agents are generally safe and well tolerated, these medications only induce remission in approximately 50% of patients with UC (2). Corticosteroids, azathioprine/6-mercaptopurine, and cyclosporine are each associated with significant risks of complications ranging from systemic infections to avascular necrosis. Furthermore, not all patients respond to these medications. As such, there is a great need for additional therapies to treat patients with UC refractory to 5-ASA agents.

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor superfamily of transcription factors whose activities are regulated by high affinity binding of small lipophilic ligands such as steroid hormones (3). A new class of antidiabetic drugs, the thiazolidinediones, has been developed that bind to the γ subtype of the PPARs. Colonic epithelial cells express high levels of PPARγ protein (4) and have the ability to produce inflammatory cytokines that may contribute to the inflammatory process in UC. We have previously demonstrated that PPARγ ligands significantly attenuate cytokine gene expression in colon cancer cell lines by inhibiting the activation of nuclear factor κ B (NF-κB) via an inhibitor of NF-κB–dependent mechanism (5). Furthermore, other investigators and we have demonstrated that thiazolidinedione ligands for PPARγ markedly reduce colonic inflammation in two different murine models of colitis (5, 6). These *in vitro* and *in vivo* data suggest that PPARγ ligands may have a therapeutic effect in UC. This study was designed to examine the potential efficacy of PPARγ ligands as therapy for mild to moderately active UC.

MATERIALS AND METHODS

Design

We enrolled 15 patients with mild to moderately active UC in an open-labeled prospective single-arm study of rosiglitazone (Avandia) (4 mg *p.o. b.i.d.*) for 12 wk. Patients were evaluated at 0, 2, 4, 8, and 12 wk for response to therapy and evidence of adverse events. In addition, patients underwent flexible sigmoidoscopy at the week 0 and week 12 visits.

Table 1. Components of the DAI

Stool frequency
0 = normal
1 = 1–2 stools/day more than normal
2 = 3–4 stools/day more than normal
3 = >4 stools/day more than normal
Rectal bleeding
0 = none
1 = streaks of blood
2 = obvious blood
3 = mostly blood
Mucosal appearance
0 = normal
1 = mild friability
2 = moderate friability
3 = exudation, spontaneous bleeding
Physician rating of disease activity
0 = normal
1 = mild
2 = moderate
3 = severe

Inclusion and Exclusion Criteria

All patients had UC documented on the basis of a combination of clinical, endoscopic, radiographic, and/or histological findings. Only patients with mild to moderately active UC despite a minimum of 4 wk of therapy with at least 3 g daily of an oral 5-ASA compound were eligible for inclusion. Disease activity was assessed using a previously described Disease Activity Index (DAI) (7–11). This index is calculated by summing the score of four factors, each of which is graded on a scale from 0 to 3 (Table 1). The four features of disease activity are stool frequency, bleeding, physician's assessment of disease activity, and mucosal appearance. The maximum potential score is 12 points, with higher scores representing more severe disease. Mild to moderate disease activity was defined as a score of 4–10 inclusive.

We permitted concomitant therapy with corticosteroids as long as the steroid dose was stable for a minimum of 4 wk before enrollment. Concomitant therapy with azathioprine or 6-mercaptopurine was allowed as long as the patient had been receiving the medication for a minimum of 24 wk and was on a stable dose for a minimum of 12 wk before enrollment. No patients received concomitant therapy with rectally administered corticosteroids or 5-ASA compounds. Steroids could be tapered during the study at the discretion of the treating physician. Use of antidiarrheal medications was not permitted.

Patients were excluded if they had evidence of infectious colitis on the basis of stool culture, examination for ova and parasites, or detection of *Clostridium difficile* toxin. In addition, patients were excluded if they had acute or chronic liver disease, abnormal liver-associated chemistries, a contraindication to flexible sigmoidoscopy or biopsy, New York Heart Association class III or IV heart failure, an active malignancy other than nonmelanoma skin cancer, or diabetes mellitus requiring medical therapy.

Table 2. Characteristics of the 15 Patients Enrolled in the Study

Male (%)	12 (80)
Age (yr, median and range)	46 (26–71)
Years with UC (median and range)	4 (1–40)
Distribution of disease (%)	
Proctitis	1 (7)
Left-sided disease	5 (33)
Extensive disease	9 (60)
Weeks on current 5-ASA dose (median and range)	36 (4–260)
Concomitant steroids (%)	8 (53)
Concomitant azathioprine or 6-mercaptopurine (%)	7 (47)
DAI score (median and range)	8 (4–9)

Definition of Outcomes

We examined several outcomes in our study. Patients with a final DAI score of ≤ 2 points were considered to have achieved clinical remission. A partial response was defined as a reduction in the DAI of ≥ 2 points, but with a final score of ≥ 3. Endoscopic remission was defined as a clinical remission plus a final score of 0 on the mucosal appearance subscale of the DAI.

Because flexible sigmoidoscopy was only completed at the initial and final visit, it was not possible to calculate a DAI score at each time point. However, we computed a modified DAI score that includes all components of the full DAI score except the endoscopic appearance of the bowel. The maximum potential score in the modified DAI is 9.

Statistical Analysis

Descriptive data are reported as percentages and medians and ranges. The paired *t* test was used to compare average DAI scores at different time points. All analyses used two-sided tests of statistical significance with a significance level of 0.05. Statistical analyses were performed using STATA 6.0 (Stata, College Station, TX).

RESULTS

The prestudy characteristics of these patients are summarized in Table 2. Fifteen patients (12 male) were enrolled in the study. The median age was 41 yr (range = 26–71) and the median duration of UC was 4 yr (range = 1–40). The extent of disease was proctitis in one (7%), left-sided in five (33%), and extensive in nine (60%). All but two patients were treated with either corticosteroids or immunomodulators in addition to 5-ASA agents before enrolling in the study. At enrollment, the median DAI score was 8 (range = 4–9).

The outcomes of the 15 patients who enrolled in the study are depicted in Figure 1. Clinical remission was achieved in four of 15 patients (27%), two of whom had a final score of 0 and three of whom were classified as having an endoscopic remission. Four additional patients (27%) achieved a partial response. Thus eight patients (53%) achieved either a clinical remission or a partial response. At the conclusion of the trial, six of the eight responders elected to continue to receive rosiglitazone off protocol. All but one of these

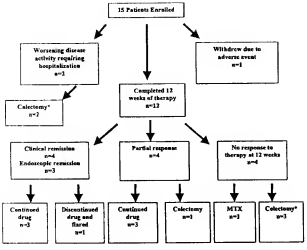

Figure 1. Outcome of 15 patients enrolled in the trial. Three patients were withdrawn early, two because of worsening disease activity and one because of a serious adverse event. Eight patients responded to therapy, four achieving a clinical remission (three with endoscopic and clinical remission) and four with a partial response. MTX = methotrexate. *Of the seven patients who failed to respond to therapy, three have undergone colectomy and two others were advised to undergo colectomy.

patients continued to do well after a median follow-up of 29 wk (range = 16–41). A single patient in remission at the conclusion of the study discontinued therapy and subsequently relapsed 8 wk later. Another partial responder underwent an elective colectomy for persistent symptoms.

Eight patients were receiving corticosteroids at the start of the study (median daily prednisone dose = 20 mg, range = 5–40). At the conclusion of the study, these patients' median daily dose was 2.5 mg (range = 0–20). Six of the eight patients initially receiving corticosteroids had reduced their daily dose by 50% or more. Of the other two patients, one was withdrawn early because of worsening disease activity. This patient's prednisone dose remained at 20 mg for the entire time the patient was in the study. The other patient received 5 mg daily throughout the entirety of the study.

Of the seven patients classified as nonresponders, two required hospitalization for worsening disease activity while on therapy. Three of the seven nonresponders have undergone colectomy, all for chronically active disease that was refractory to medical therapy rather than fulminant colitis. Two others were advised to undergo colectomy by their physicians.

In a secondary analysis, we examined the change in the DAI and the modified DAI over time (Fig. 2). There was a significant decrease in the mean DAI score for patients completing 12 wk of therapy (Fig. 2A) ($p = 0.01$). The modified DAI includes all components of the full DAI except the mucosal appearance score and can be calculated at each study visit (Fig. 2B). The average modified DAI score was significantly lower than at baseline for patients remaining in the trial by week 4 and remained significantly lower for the remainder of the study ($p = 0.007$ at week 4, $p = 0.026$ at week 8, $p = 0.005$ at week 12).

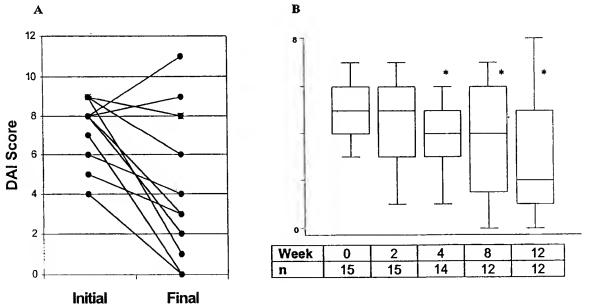

Figure 2. *(A)* Change in DAI from week 0 to week 12. Patients who were withdrawn early from the study are not included. The initial DAI scores were 5 and 6 for the two patients hospitalized for increased disease activity and 7 for the patient with nephrotic syndrome. There was a significant decrease in the mean DAI score for patients completing 12 wk of therapy ($p = 0.01$). *(B)* Change in the modified DAI. A modified DAI score, including all components of the complete DAI other than the endoscopic appearance, can be calculated at each observation point. The maximum potential score in the modified DAI is 9. By week 4, the mean modified DAI score was significantly lower than at baseline for patients remaining in the trial ($p = 0.007$ at week 4, $p = 0.026$ at week 8, $p = 0.005$ at week 12).

Adverse Events

Four patients reported serious adverse events during the study. As previously described, two patients required hospitalization for worsening disease activity. One patient developed nephrotic syndrome approximately 8 wk into therapy and was withdrawn from the study. A kidney biopsy was consistent with minimal change disease. The patient was treated with corticosteroids and has had complete resolution of his proteinuria.

Another patient developed severe group A streptococcal pharyngitis and aseptic arthritis during his final week of therapy. Because of the severity of the pharyngitis despite 3 days of oral antibiotics, the patient was admitted to hospital for *i.v.* antibiotics and corticosteroids. He rapidly responded to this therapy and was discharged to home within 24 h of admission. The patient completed the study 3 days later and was classified as a partial responder (final score = 3). This patient's UC had clinically responded before the onset of his pharyngitis, and he elected to continue the study medication after completing the trial.

One additional patient developed mild, transient lower extremity edema. No patient developed abnormal liver chemistries during the course of the study.

DISCUSSION

To our knowledge, this is the first reported use of a PPARγ ligand as therapy for UC in humans. In this pilot study, 27% of patients achieved a clinical remission, 20% achieved an endoscopic remission, and 53% had a clinical improvement within 12 wk of starting therapy. Because this was an open-labeled single arm study, it is not possible from our data to state with certainty that PPARγ ligands are effective as therapy for UC. Nonetheless, our results compare favorably with the observed response rates among patients with UC receiving placebo therapy in prior randomized controlled trials. Three meta-analyses and systematic reviews of the literature have been performed (12–14), each estimating that the remission rate with placebos for active UC is approximately 10%. Additionally, the estimated partial response rate with placebos is approximately 26.7% (12). Furthermore, our results were nearly identical to that achieved with transdermal nicotine in a similar patient group using the same index to measure disease activity (7). Thus, our data suggest that this class of medications may represent a novel therapy for UC.

The DAI has been widely used in other studies of UC (7–11). The index includes four parameters that are felt to define disease activity in UC. Careful examination of our data supports our definition of remission and response. All patients classified as achieving a clinical remission had a final score of 0 (remission) for the physician rating of disease activity and bleeding subscales. Similarly, all patients classified as responders had a decrease in the physician rating of disease activity and bleeding. Seven of the eight responders had a decrease in stool frequency, and all but two had improvement in the mucosal appearance. Finally, three of the four partial responders requested continuation of the medication off protocol at the conclusion of the study. Thus, the responders appeared to have had a clinically meaningful improvement in disease activity, and this improvement was evident in all features measured by the DAI.

The patients included in our trial all had relatively refractory UC. Each patient had active disease despite a minimum of 4 wk of therapy with at least 3 g *p.o.* of a 5-ASA compound. In addition, 87% of our patients were receiving steroids and/or immunomodulator therapy immediately before enrolling in the study. Further evidence of the refractory nature of our patients' disease is the high proportion of nonresponding patients who have either undergone or been recommended to undergo colectomy. Importantly, none of these subjects underwent colectomy for fulminant colitis but, rather, refractory UC. In addition, one patient scheduled to undergo elective colectomy elected to postpone surgery and enroll in this study. Having achieved a partial response, this patient continued therapy with rosiglitazone and has sustained clinical improvement 29 wk beyond the conclusion of the study period.

Concern has been raised about the safety of this class of medications, particularly with respect to liver toxicity (15). None of our patients developed abnormal liver enzymes during therapy. However, we excluded all patients with evidence of acute or chronic liver disease.

Other than worsening disease activity, two patients experienced serious adverse events during the study. One patient developed minimal change disease of the kidneys that responded rapidly to steroids. We are unaware of any previous reports of nephrotic syndrome associated with PPARγ ligand therapy. However, this patient was also receiving 5-ASA therapy, which has been reported to cause minimal change disease (16, 17). From the currently available data it is not possible to state with certainty whether the nephrotic syndrome was a consequence of therapy with rosiglitazone.

The other patient experiencing a serious adverse event developed a severe streptococcal pharyngitis. Whether the severity of this pharyngitis was a result of therapy with rosiglitazone is also unclear, as this patient was also receiving 75 mg of 6-mercaptopurine daily. It should be noted that in premarketing studies of a related compound, pioglitazone (Actos), pharyngitis was reported more commonly by those patients receiving the active drug as opposed to a placebo (5.1% *vs* 0.8%) (18). Certainly, researchers in future studies should be aware of this as a potential drug-related side effect.

We are aware of one serious adverse event that occurred after the study was completed. The same patient who developed the severe pharyngitis requested from his primary physician that he be allowed to remain on the medication after the study was completed. Approximately 188 days after initiating therapy with rosiglitazone, this patient was admitted to hospital with a fatal intracerebral hemorrhage. His platelet count and coagulation parameters were normal

at the time of admission to hospital. We are unaware of any reported association between this class of medications and intracerebral hemorrhage. Nonetheless, we cannot completely exclude that his medical therapy may have in some way contributed to this event.

Our data suggest that some patients may require as much as 12 wk to achieve a clinical response. This is consistent with the time to effect of these compounds when used to treat diabetes mellitus. The antidiabetic effects of PPARγ ligands are noticeable at 4 wk but may not reach their maximum effect until 12 wk or later (19).

The exact mechanism of action by which PPARγs exert their anti-inflammatory effects in the colon remains unclear. We have previously shown that PPARγ ligands significantly attenuate cytokine gene expression in colon cancer cell lines by inhibiting the activation of NF-κB via an inhibitor of NF-κB–dependent mechanism (5). However, recent studies have shown that certain ligands for PPARγ, such as cyclopentanone prostanoids, may exert their anti-inflammatory effects through a PPARγ-independent pathway (20). Other investigators have suggested that the anti-inflammatory activity of these agents may be mediated through inhibition of tumor necrosis factor α–signaling pathways (6). Importantly, thiazolidinedione ligands for PPARγ demonstrate impressive anti-inflammatory activity in two animal models of colitis commonly used to screen pharmacological agents for the treatment of patients with UC (5, 6). Furthermore, a very recent study has demonstrated that treatment of mice with a PPARγ ligand reduced the severity of intestinal injury in a murine model of ischemia-reperfusion injury (21). Importantly, they also show that genetically engineered mice, which express lower levels of PPARγ, experience more severe intestinal injury in this same model, providing direct genetic evidence for an immunoregulatory role for this nuclear hormone receptor. Clearly, further defining the mechanism by which these agents exhibit their anti-inflammatory activity in the intestine should remain an important focus of future research.

New therapies for UC are needed. For those patients whose disease fails to respond to therapy with a 5-ASA agent, the options are relatively limited. Unfortunately, many of these patients will fail to respond even to a combination of 5-ASA and steroids or immunomodulator medications. Our results suggest that patients with mild to moderately active disease refractory to these standard therapies may benefit from therapy with PPARγ ligands. As such, we believe that a double blind, placebo-controlled, randomized trial of these agents for mild to moderately active UC is warranted.

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REFERENCES

1. Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults. American College of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol 1997;92:204–11.
2. Sutherland LR, May GR, Shaffer EA. Sulfasalazine revisited: A meta-analysis of 5-aminosalicylic acid in the treatment of ulcerative colitis. Ann Intern Med 1993;118:540–9.
3. Mangelsdorf DJ, Thummel C, Beato M, et al. The nuclear receptor superfamily: The second decade. Cell 1995;83:835–9.
4. Fajas L, Auboeuf D, Raspe E, et al. The organization, promoter analysis, and expression of the human PPARgamma gene. J Biol Chem 1997;272:18779–89.
5. Su CG, Wen X, Bailey ST, et al. A novel therapy for colitis utilizing PPAR-gamma ligands to inhibit the epithelial inflammatory response. J Clin Invest 1999;104:383–9.
6. Dubuquoy L, Bourdon C, Peuchmaur M, et al. Peroxisome proliferator-activated receptor (PPAR) gamma: A new target for the treatment of inflammatory bowel disease. Gastroenterol Clin Biol 2000;24:719–24.
7. Sandborn WJ, Tremaine WJ, Offord KP, et al. Transdermal nicotine for mildly to moderately active ulcerative colitis. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1997;126:364–71.
8. Sutherland LR, Martin F. 5-Aminosalicylic acid enemas in treatment of distal ulcerative colitis and proctitis in Canada. Dig Dis Sci 1987;32:64S-6S.
9. Sutherland LR, Martin F, Greer S, et al. 5-Aminosalicylic acid enema in the treatment of distal ulcerative colitis, proctosigmoiditis, and proctitis. Gastroenterology 1987;92:1894–8.
10. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med 1987;317:1625–9.
11. Roberts WG, Simon TJ, Berlin RG, et al. Leukotrienes in ulcerative colitis: Results of a multicenter trial of a leukotriene biosynthesis inhibitor, MK-591. Gastroenterology 1997;112:725–32.
12. Ilnyckyj A, Shanahan F, Anton PA, et al. Quantification of the placebo response in ulcerative colitis. Gastroenterology 1997;112:1854–8.
13. Kornbluth AA, Salomon P, Sacks HS, et al. Meta-analysis of the effectiveness of current drug therapy of ulcerative colitis. J Clin Gastroenterol 1993;16:215–8.
14. Cohen R, Woseth D, Thisted R, Hanauer S. A meta-analysis and overview of the literature on treatment options for left-sided ulcerative colitis and ulcerative proctitis. Am J Gastroenterol 2000;95:1263–76.
15. Forman LM, Simmons DA, Diamond RH. Hepatic failure in a patient taking rosiglitazone. Ann Intern Med 2000;132:118–21.
16. Novis BH, Korzets Z, Chen P, Bernheim J. Nephrotic syndrome after treatment with 5-aminosalicylic acid. Br Med J (Clin Res Ed) 1988;296:1442.
17. Barbour VM, Williams PF. Nephrotic syndrome associated with sulphasalazine. BMJ 1990;301:818.

18. Pioglitazone (package insert). Lincolnshire, IL: Takeda Pharmaceuticals North America, 2000.
19. Fonseca V, Rosenstock J, Patwardhan R, Salzman A. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: A randomized controlled trial. JAMA 2000;283:1695–702.
20. Rossi A, Kapahi P, Natoli G, et al. Anti-inflammatory cyclopentenone prostaglandins are direct inhibitors of IkappaB kinase. Nature 2000;403:103–8.
21. Nakajima A, Wada K, Miki H, et al. Endogenous PPARγ mediates anti-inflammatory activity in murine ischemia-reperfusion injury. Gastroenterology 2001;120:460–9.